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Systematic or Meta-analysis Studies

Clinical benefit of controversial first line systemic therapies for advanced stage ovarian cancer – ESMO-MCBS scores

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ABSTRACT

Background: The magnitude of clinical benefit scale (MCBS) was introduced by the European Society of Medical Oncology (ESMO) to quantify the clinical benefit of therapeutic regimens and to prioritise therapies. It distinguishes curative from palliative treatments and ranks their benefit based on overall survival (OS), progression free survival (PFS), quality of life (QoL) and toxicity. Objective of this study on the first line treatment of ovarian cancer was to evaluate the evidence for the current standard of care using the ESMO-MCBSv1.1 with an emphasis on controversial therapeutic options: intraperitoneal chemotherapy, dose-dense paclitaxel and bevacizumab.

Methods: Phase III trials, published since 1992, investigating first line systemic treatment of Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage IIB-IV epithelial ovarian cancer were included. Since most studies included patients with FIGO stage IV disease or incomplete debulking, all treatments were judged to be palliative. Treatments were graded 5 to 1 on the ESMO-MCBSv1.1, where grades 5 and 4 represent a high level of clinical benefit.

Results: 55 studies met the inclusion criteria. ESMO-MCBS scores were calculated for eleven studies that showed a statistically significant benefit of the experimental treatment. Intraperitoneal (ip) cisplatin scored a 4 and 3, but two other studies were negative and therefore not scored on the ESMO-MCBS. Dose-dense paclitaxel showed substantial clinical benefit in one study (score 4), but three studies were negative. Addition of bevacizumab also scored a 4 in one study subgroup including high-risk patients but a 2 in another trial with a larger study population.

Conclusion: Based on ESMO-MCBS scores, dose-dense paclitaxel and intraperitoneal chemotherapy cannot be recommended as standard treatment. Bevacizumab should be considered only in the high-risk population. The ESMO-MCBSv1.1. helps to summarise reported studies on controversial treatment regimens, and identifies their weaknesses.

Introduction

Epithelial ovarian cancer has the highest mortality of all gynaecological cancers [1]. The disease is often diagnosed at a late stage because symptoms only develop once the disease has spread throughout the abdominal cavity. However, even in case of advanced stage disease, long-term survival is possible [2]. First line therapy for advanced disease consists of complete debulking surgery in combination with chemotherapy (carboplatin and paclitaxel given every 3 weeks). Despite extensive research, only few therapies with proven clinical benefit have been added to the therapeutic arsenal during the past decades (Fig. 1). The total costs of ovarian cancer treatment have, however, increased and vary greatly between European countries, partly due to differences in use of both chemotherapeutic and targeted drugs [3,4]. European Society of Medical Oncology (ESMO) clinical practice guidelines [5] and National Comprehensive Cancer Network (NCCN) guidelines [6] label several first line therapies such as intraperitoneal (ip) cisplatin, dose-dense weekly paclitaxel plus 3-weekly carboplatin, and bevazicumab maintenance therapy as 'optional'. The recent debate on the addition of bevacizumab to first line treatment of advanced ovarian cancer is exemplary for differing policies between European countries with respect to use of new drugs [7].

The inclusion of therapeutic strategies in health insurance plans and health-care outcomes vary significantly between countries [8–12].

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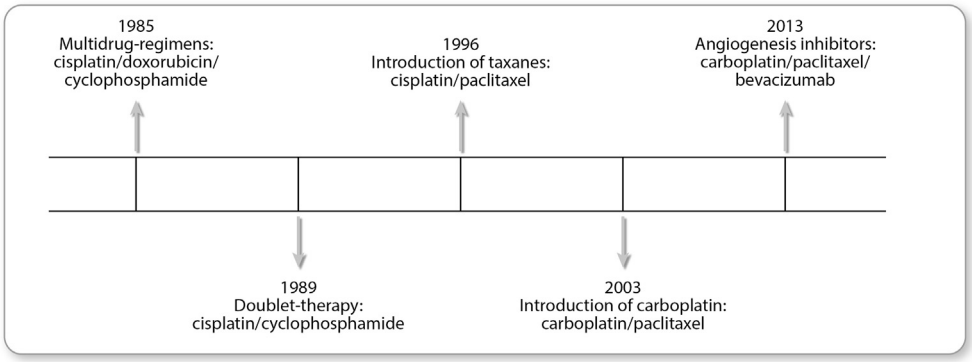

Fig. 1. Evolution of standard first line systemic therapy in advanced ovarian cancer.

Some therapies provide only a small incremental benefit despite risks of serious toxicity. This makes careful consideration of their value for the quality of life (QoL) of patients and health care costs for society essential. ESMO has developed and validated a tool to assess the magnitude of clinical benefit of cancer medicines: the Magnitude of Clinical Benefit Scale (MCBS) [13,14]. The aim of the ESMO-MCBS is to prioritise the most beneficial treatments and make them available for all patients in Europe. The ESMO-MCBS was designed to rank new drugs based on adequately powered trials, taking into account differences in study design and reported treatment effects. Future anti-cancer drugs or treatments that are approved by the European Medicines Agency (EMA) will be evaluated using the ESMO-MCBS, and interventions showing substantial benefit will be highlighted in the ESMO guidelines. The objective of this study was to re-evaluate the evidence regarding first line treatment of ovarian cancer using the ESMO-MCBSv1.1 with focus on intraperitoneal chemotherapy, dose-dense paclitaxel and bevacizumab.

Methods

Search strategy and scoring

Published, phase III, randomised controlled trials (RCT's) investigating first line systemic treatment of Fédération Internationale de Gynécologie et d'Obstétrique (FIGO) stage IIB-IV ovarian cancer were identified by a PubMed search. The search terms used were: ovarian neoplasms, ovarian cancer, drug therapy, chemotherapy, advanced stage; results were filtered for clinical trials on humans. References of selected articles as well as the Cochrane Library Systematic Reviews and the relevant international guidelines were cross-checked for additional published studies. Studies published from 1992, the introduction of taxanes [15], until March 2018 were included. For studies reporting impending long-term survival data, PubMed was additionally searched specifically for publication of this data. The search was performed independently by two authors (MJ and KEB), in case of different search results these were discussed in the presence of a third investigator (AKLR). For all studies reporting a statistically significant benefit of the experimental treatment over the comparator, the magnitude of clinical benefit was scored by two separate authors (KEB and MJ) on the ESMO-MCBSv1.1. In case of discussion or discrepancy between these two authors' scores, the judgment of a third author was decisive (AKLR). For studies not reporting a statistically significant benefit of the study treatment an ESMO-MCBS score could not be given.

ESMO-MCBS

The ESMO-MCBS [13,14] ranks the value of new cancer therapies in a structured manner, by taking into account reported benefits in terms of longer survival (progression free survival (PFS), disease-free survival (DFS), overall survival (OS)) and better survival (e.g. QoL, toxicity). To make a comparison possible between trials with different methods, different control groups and endpoints, there are separate scoring forms divided by endpoint and duration of survival of the control group. First, there are separate forms for curative (form 1) and palliative treatments (form 2). Curative or adjuvant treatments are graded A, B or C, with grade A and B corresponding to a substantial clinical benefit. The highest score (A) is given for $> 5\%$ improvement of OS at ≥ 3 years, or for improvement of DFS with a hazard ratio (HR) lower limit < 0.65 when mature survival data are lacking. For palliative treatments there are forms for studies with a primary endpoint of OS (form 2a), PFS (form 2b) or QoL, toxicity or response rate (RR) (form 2c). Palliative treatments are graded 5 to 1, where grades 5 and 4 represent a substantial clinical benefit. Recently, a revised version of the ESMO-MCBS was published [14]. In ESMO-MCBSv1.1 a new form 3 was introduced for scoring of single-arm studies in "orphan diseases" and for diseases with "high unmet need" leading to registration of the treatment studied. Furthermore, the threshold for absolute gain in median OS resulting in a score of 5 or 4 was set higher (i.e. more conservative, at 9 months instead of 5 months) for studies with a median survival in the control arm of more than 2 years. The preliminary score for palliative treatments is upgraded when the study treatment shows an improvement in QoL or a reduction in grade 3–4 toxicities impacting on daily well-being. When PFS is the primary endpoint, the preliminary score is downgraded when the study treatment has increased toxicity or does not demonstrate improvement in QoL. All ESMO-MCBS forms can be downloaded online (http://www.esmo.org/Policy/Magnitude-of-Clinical-Benefit-Scale).

It can be debated whether treatment of stage IV ovarian cancer, with five-year overall survival of approximately 20%, should be considered curative or palliative. Cure rate depends on the amount of residual disease after surgery. This factor is highly variable, and besides patient and tumour related factors, depends on the surgeon's skills, the location of treatment and the time period in which the study was performed [16]. In this analysis, most studies included patients with stage IV disease and allowed patients with residual masses after debulking surgery to enter. Therefore, all treatments studied in the included trials were labelled 'with palliative intent'.

Validity of included studies

To evaluate the quality and robustness of the included studies and compare studies with and without substantial benefit on the ESMO-MCBS, a Cochrane Institute validity checklist was used [17]. This checklist is a synthesis of the Cochrane Collaboration risk of bias tool [18] and contains ten items that are also included in the CONSORT statement on reporting of RCTs [19] (Supplementary Table 1). It is designed to visualise the validity of studies included in a systematic review, but not to rank them based on a sum score. Weighing of the

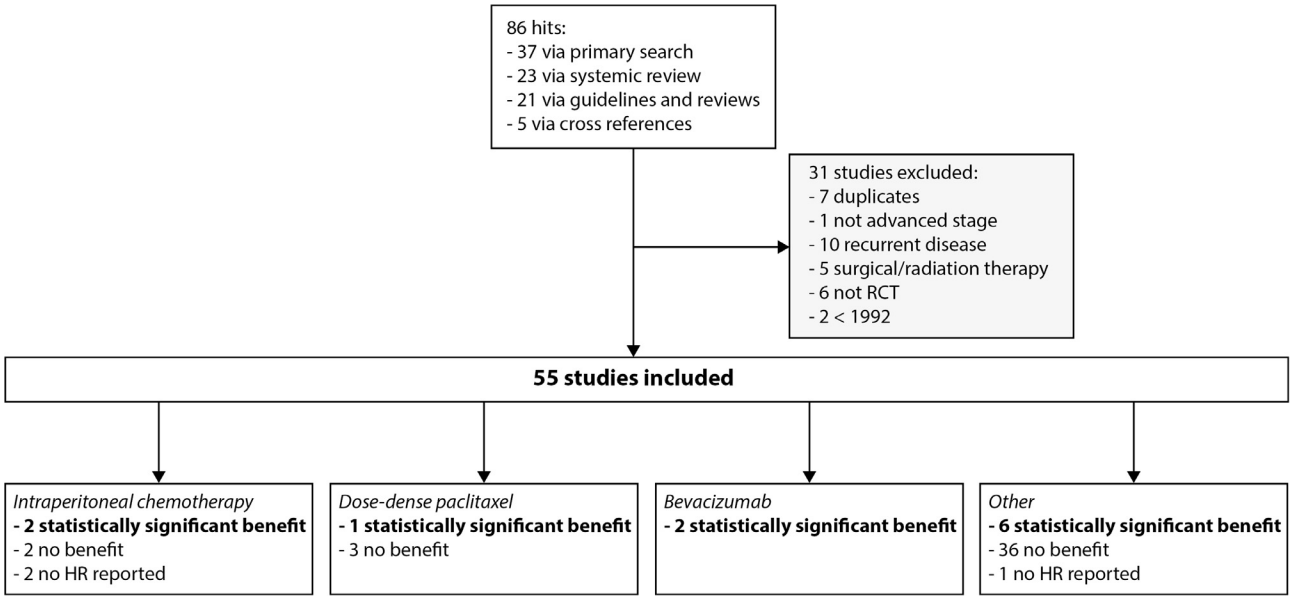

Fig. 2. Flow diagram of studies included for analysis according to the ESMO-MCBSv1.1. RCT = randomised controlled trial; HR = hazard ratio.

different items is not incorporated in the checklist; hence there are no threshold values for low or acceptable validity.

Results

The search resulted in 86 hits, of which 55 unique phase III trials met the inclusion criteria. Of these studies, 44 investigated first line therapy and 11 investigated maintenance therapy after first line therapy. There were no single-arm trials leading to registration of the studied treatment in advanced ovarian cancer. QoL data was available for 18 of 55 included studies. Thirteen studies investigating first line treatment and one study on maintenance therapy showed a statistically significant benefit of the experimental treatment. Three of these studies reported a relative risk (RR) only and not a HR, therefore the ESMO-MCBS score could not be calculated. As a result, ESMO-MCBS scoring was performed for eleven of the 55 studies (Fig. 2).

Studies on controversial first line treatments: Intraperitoneal chemotherapy, dose-dense paclitaxel and bevacizumab

Table 1 shows the included studies on intraperitoneal chemotherapy, dose-dense paclitaxel and bevacizumab. Studies showing statistically significant benefit were scored using the ESMO-MCBSv1.1. Ip administration of cisplatin achieved a score of 3 and 4 on ESMO-MCBSv1.1 [20,21]. There were two negative studies on ip treatment [22,23]. Dose dense administration of paclitaxel (80 mg/m^2 q1w) compared to conventional dose paclitaxel (180 mg/m^2 q3w) is supported by one study (score 4) [24]. Three negative studies on weekly paclitaxel were identified [25–27]. The addition of bevacizumab to carboplatin and paclitaxel scored a 2 [28] and a 4 [29]. The score of 4 was achieved only in a high-risk population, defined as stage IV disease, inoperable stage III disease, or suboptimally debulked (> 1 cm) stage III disease.

Standard of care options

The current standard first line treatment with carboplatin and paclitaxel is supported by five studies [30–34]. In these five studies carboplatin and paclitaxel were compared to cisplatin with or without cyclophosphamide, the standard of care at that time. ESMO-MCBSv1.1 scores are 4, 4, 4, 3 and 4 respectively. Four of the studies showed comparable survival but a better QoL [32] or toxicity profile [30,31,33] of the experimental treatment, one study showed an OS benefit [34].

Other studies

Studies investigating other chemotherapeutic agents, anti-hormonal therapy or immune modulating therapies did not show a statistically significant benefit of the experimental treatment over the comparator, nor a better QoL or toxicity profile and are therefore not indicated in the first line treatment of ovarian cancer.

Of the 11 studies investigating maintenance therapy, only pazopanib maintenance treatment showed a statistically significant benefit over the control arm (no maintenance treatment). However, the clinical benefit of maintenance therapy with pazopanib after surgical debulking and first line treatment with carboplatin and paclitaxel could not be qualified as 'substantial', with a score of 2 [35].

Table 2 shows the 6 positive studies (5 carboplatin/paclitaxel and 1 pazopanib). All the negative studies on the current standard of care and other treatment regimens are shown in Table 3 [36–71].

The three studies that did not report a HR are summarised in Supplementary Table 2 [72–74]. It concerns one study comparing paclitaxel/cisplatin to cyclophosphamide/cisplatin and two studies investigating ip cisplatin.

Validity of included studies

Validity scores of the 55 included phase III studies are shown in Tables 4a and 4b. Nine studies fulfilled 5 or less of 10 criteria on the Cochrane Institute checklist. Six of these were studies performed before 2000. One of these nine studies showed clinical benefit of carboplatin over cisplatin [31] while the other eight studies did not report clinically meaningful benefits of the experimental treatment. The studies supporting ip administration of cisplatin score 6 out of 10 validity criteria [20,21], as does one study supporting carboplatin over cisplatin added to paclitaxel [33]. All the other studies scored on the ESMO-MCBSv1.1 fulfilled more than 6 validity criteria.

The two studies showing a statistically significant benefit of ip cisplatin but not reporting a HR fulfilled 6/10 validity criteria (Supplementary Table 3). Importantly, ip administration of cisplatin was not the only difference between the control and the intervention arm in these studies. Two doses of carboplatin were added to ip

Table 1

Trials on intraperitoneal chemotherapy, dose-dense paclitaxel and bevacizumab. * if no tumor type specified only EOC patients were included; cm = centimeters; EOC = epithelial ovarian cancer; FTC = fallopian tube cancer; Gr = grade; HR = hazard ratio; ip = intraperitoneal; iv = intravenous; mth = months; ns = not significantly different; OS = overall survival; PFS = progression free survival; PPC = primary peritoneal cancer; QoL = quality of life; RM = residual mass; vs = versus.

Trial name/ first author	Year	Setting	Drug control vs intervention (n)	Primary outcome / design	PFS control	PFS Gain	PFS HR	OS control	OS Gain	OS HR	QoL	Toxicity control vs intervention	ESMO-MCBS v1.1
Intraperitoneal chemotherapy													
Alberts [20]	1996	Stage III after debulking (RM < 2 cm)	Cisplatin iv / cyclophosphamide (n=279) vs cisplatin ip / cyclophosphamide (n=267)	OS				41 mth	8 mth	0.76 (0.61-0.96)		Gr 3-4 neutropenia 69 vs 56% Gr 3-4 abdominal pain 2 vs 18% Gr 3-4 hearing loss 15 vs 5% Gr 3-4 neurotoxicity 25 vs 15%	3
Van Driel [21]	2018	Stage III EOC, FTC, PPC; at least stable diseae after 3 cycles of neo-adjuvant treatment	Intervaldebulking (n=123) vs intervaldebulking with HIPEC cisplatin 100mg/m2 (n=122)	PFS OS key secondary				33.9 mth	11.8 mth	0.67 (0.48-0.94)	EORTC QLQ ns	Comparable	4
Kirmani [22]	1994	Stage IIC-IV after debulking	Cisplatin iv / cyclophosphamide iv (n=33) vs cisplatin ip / etoposide ip (n=29)	Complete response rate									
Gadducci [23]	2000	Stage IIC-IV after debulking (RM<2 cm)	Cisplatin / epidoxorubicin / cyclophosphamide iv (n=57) vs cisplatin ip / epidoxorubicin iv / cyclophosphamide iv (n=54)	OS Crossover ip-iv									
Dose-dense paclitaxel													
JGOG 3016 / Katsumata [24]	2013	Stage II-IV EOC, FTC, PPC	Carboplatin / paclitaxel conventional dose (n=319) vs dose dense (n=312)	PFS OS secondary but data mature				62 mth	38 mth	0.79 (0.63-0.99)		Anemia 44 vs 69% Neuropathy ns	4
Pignata [25]	2014	Stage Ic-IV after debulking	Carboplatin /paclitaxel conventional dose (n=404) vs dose dense (n=406)	PFS + QoL									
Chan [26]	2016	Stage II-IV EOC, FTC, PPC before / after debulking	Carboplatin / bevacizumab optional / paclitaxel conventional dose (n=346) vs dose dense (n=346)	PFS									
ICON8 [27]	2018	Stage IC high risk – IV EOC, FTC, PPC	Carboplatin /paclitaxel conventional dose vs carboplatin / dose dense paclitaxel vs carboplatin AUC 2 weekly / dose dense paclitaxel	PFS									
Bevacizumab													
GOG 218 / Burger [28]	2011	Stage III or IV EOC, FTC, PPC after debulking	Carboplatin / paclitaxel / placebo (n=625) vs carboplatin / paclitaxel / bevacizumab cycle 2-6 (n=625) vs carboplatin / paclitaxel / bevacizumab cycle 2-22 (n=623)	PFS OS data immature	10.3 mth	0.9 mth bevacizumab cycle 2-6 3.8 mth bevacizumab cycle 2-22	0.72 (0.63-0.82) bevacizumab cycle 2-22				FACT-O ns	Gr 2-4 hypertension 7.2 vs 22.9%	2
ICON-7 / Oza [29]	2015	Stage I-IIA (high risk) or stage IIB-IV EOC, PPC, FTC	Carboplatin /paclitaxel (n=254) vs carboplatin /paclitaxel / bevacizumab (n=248)	OS Prespecified subgroup analysis high risk patients				30.2 mth	9.5 mth >10% OS gain at 3 years 4.4% OS gain at 5 years	0.78 (0.63-0.97)	EORTC QLQ ns		4

cisplatin and iv paclitaxel in the experimental arm in one study [72], and in the other study an extra dose of paclitaxel was given per patient in the intervention arm [73]. Two included negative studies (therefore not scored on the ESMO-MCBSv1.1) on ip cisplatin treatment scored low on the validity checklist: 4/10 and 5/10 [22,23].

Discussion

Based on ESMO-MCBS scores, intraperitoneal chemotherapy and dose-dense paclitaxel cannot be recommended as standard treatment. Addition of bevacizumab to first line chemotherapy only showed substantial clinical benefit in a high-risk subgroup of patients (stage IV disease, inoperable stage III disease, or suboptimally debulked (> 1 cm) stage III disease).

Ip chemotherapy using cisplatin does not provide substantial benefit as first line treatment of advanced ovarian cancer according to the score of 3 on the ESMO-MCBSv1.1 [20]. This is the only treatment with a downgraded score (from 4 to 3) on v1.1 of the ESMO-MCBS compared to v1.0. The difference between the two scores is due to the more restrictive criteria for 'substantial benefit' on ESMO-MCBSv1.1 (absolute gain ≥9 months) compared to version 1.0 (absolute gain ≥5 months) [14]. Recently, the results of another study were published [21], showing an improvement of recurrence-free survival (RFS) and OS of the addition of hyperthermic intraperitoneal chemotherapy (HIPEC) with cisplatin 100 mg/m2 to interval debulking surgery in stage III ovarian cancer patients not progressing after neo-adjuvant chemotherapy. These outcomes give a score of '4' on the ESMO-MCBS. However, several questions remain, making these results mainly hypothesis-generating and not yet practice-changing at this time [75]. It is unclear whether the extra dose of cisplatin could have caused the observed benefits, and whether hyperthermia is essential for an effect of ip treatment. Furthermore, the results cannot be extrapolated to other populations, such as stage IV patients, patients eligible for primary debulking surgery or patients living in areas with less HIPEC experience. Ip cisplatin is mentioned as optional in guidelines, but it has not been widely adopted. Arguable quality of the available evidence and toxicity are the main arguments against use of ip chemotherapy in an ongoing debate about this treatment modality [76]. OS-results of the large GOG-252 trial comparing dose-dense iv paclitaxel, iv carboplatin and iv bevacizumab (standard arm) to either dose-dense iv paclitaxel, ip carboplatin and iv bevacizumab or iv paclitaxel q3w, ip cisplatin and ip paclitaxel and iv bevacizumab are awaited. However, unfortunately, in this study the treatment arms also differ in more than one way impairing validity [77].

Dose-dense administration of paclitaxel added to carboplatin provides substantial clinical benefit in one study [24]. However, the reported OS benefit could not be confirmed in a recent meta-analysis including three analysed studies (not ICON8, only abstract available) [78], and the three most recent studies on dose-dense paclitaxel showed no PFS or OS-benefit [25–27]. The positive study on dose-dense paclitaxel was conducted in a Japanese patient population. Survival is suggested to be prolonged in Asian patients compared to Caucasian patients [79] potentially explained by genetic differences in drug susceptibility [80]. This might explain the different study results, and this potential bias together with the burden of weekly hospital visits and greater haematological toxicity, means that dose-dense paclitaxel cannot be recommended as part of standard first line treatment.

GOG-218 reports a benefit of adding bevacizumab to first line treatment in ovarian cancer [28], however the score of 2 on the ESMO-MCBSv1.1 does not qualify as 'substantial improvement' [13]. In ICON7 an OS benefit for addition of bevacizumab was established in the subgroup of patients at high risk of recurrence only (stage IV disease, inoperable stage III disease, or suboptimally debulked (> 1 cm) stage III disease). This prespecified subgroup analysis scored a '4' [29]. Bevacizumab was approved as a component of first line treatment by the EMA based on the benefit in these studies. However, in several countries bevacizumab has not been introduced in first line ovarian cancer treatment due to lack of data showing a consistent improvement in OS, concerns about gastro-intestinal toxicity and lack of cost-effectiveness.

The current, post-surgical, standard first line treatment of advanced ovarian cancer, combination chemotherapy with carboplatin and paclitaxel, is strongly supported by four studies that score a substantial clinical benefit on the ESMO-MCBSv1.1 [30–32,34]. There are two studies that did not show clinical benefit of paclitaxel added to platinum compared to platinum monotherapy [41,42]. Possible explanations are cross-over of about 30% from the monotherapy to the combination therapy arm, and a higher dose-intensity of carboplatin in the monotherapy arm of both studies. The largest meta-analysis of different chemotherapeutic schedules in advanced ovarian cancer (60 trials with survival endpoints, N = 15609 women) did show a survival benefit of combination therapy with a platinum and a taxane over platinum monotherapy. This meta-analysis did not only include phase III trials on first line treatment, but also randomised phase II trials and studies on second and third line treatment [81].

Pazopanib maintenance therapy showed clinical benefit based on improvement of PFS. However, due to excess toxicity leading to early treatment discontinuation in nearly one third of the patients, especially in the Asian population, pazopanib did not go into further development in the treatment of ovarian cancer [80,82].

The ESMO-MCBSv1.1 score can only be calculated when there is input of correct data. The first step in using the ESMO-MCBSv1.1 is selection of the most appropriate scoring form, by labelling the goal of the studied treatment as either curative or palliative. All treatments studied in the included trials were labelled 'with palliative intent'. However, the aforementioned criteria used to label a treatment as 'with curative' or 'palliative intent' are arbitrary and not evidence based. Seven of the studies included [24,25,33,36,58,72,73] specified multiple primary endpoints but were powered for only one, and five studies [22,45,58,65,74] did not report any power analysis. For one study [41] presented as an equivalence study a non-inferiority design was not reported, therefore scoring on the ESMO-MCBSv1.1 could not be adequately performed. Studies from the past 25 years were included in this analysis. Surgery, but also supportive care including anti-emetics and analgesics have changed over these years. This might influence the comparison of treatment results in this long time period. Current standards for study design are more robust with clear-cut guidelines for reporting results, such as hazard ratios [83]. A recent analysis of 226 contemporary RCTs showed that only one third of modern studies were designed to detect an effect size meeting the ESMO-MCBSv1.0 thresholds [84]. The current analysis includes studies with methodological shortcomings. To take into account the validity of the included studies we used a Cochrane Institute checklist for RCTs. For the six included studies on ip chemotherapy these validity scores clearly illustrate the suboptimal methodological quality of these studies. These study design weaknesses have provoked much of the debate on this treatment strategy. QoL data was only available for 18 of 55 included studies. Palliative studies showing a benefit in PFS but comparable QoL are downgraded one point (form 2B). This makes reporting of QoL data less attractive if no benefit in this endpoint is established. QoL and toxicity are especially important in treatments that are likely palliative, such as in advanced ovarian cancer. Palliative treatments showing non-inferior survival but reduced toxicity can score a '4' on the ESMO-MCBSv1.1 (form 2c). However, reduced toxicity is not clearly defined and the relative weight attributed to different toxicities remains subjective. This is a part of the ESMO-MCBS that could be further elaborated.

Recently, several other methods have been developed to determine the clinical benefit of cancer treatments. The American Society of Clinical Oncology (ASCO) published the ASCO Value Framework, a tool which incorporates clinical benefit, toxicity and also treatment costs [85]. Since the costs of the treatments in the included trials vary between countries, this tool was not used in the current analysis. Another

Table 2
Other positive trials scored for magnitude of clinical benefit on the ESMO-MCBS. * if no tumor type specified only EOC patients were included; cm = centimeters; EOC = epithelial ovarian cancer; FTC = fallopian tube cancer; Gr = grade; HR = hazard ratio; mth = months; OS = overall survival; PFS = progression free survival; PPC = primary peritoneal cancer; QoL = quality of life; RM = residual mass; vs = versus.

Trial name / first author	Year	Setting	Drug control vs intervention (n)	Primary outcome / design	PFS control	PFS Gain	PFS HR	OS control	OS Gain	OS HR	QoL	Toxicity control vs intervention	ESMO-MCBS v1.1
Hannigan [30]	1993	Stage III (RM > 2 cm) or IV after debulking	Cisplatin / cyclophosphamide (n=143) vs carboplatin / cyclophosphamide (n=148)	OS non-inferiority				17 mth	none			Gr 3-4 nausea 17 vs 8% Gr 2-4 renal toxicity 16 vs 2% Gr 2-4 hearing loss 7 vs 0% Gr 3-4 thrombocytopenia 8 vs 24%	4
Taylor [31]	1994	Stage III-IV after debulking	Cisplatin (n=64) vs carboplatin (n=67)	Response rate Crossover non-inferiority	Response duration: 21 mth	none						Crossover due to toxicity 50 vs 3%	4
OVAR-3 / DuBois [32]	2003	Stage IIB-IV after debulking	Cisplatin / paclitaxel (n=386) vs carboplatin / paclitaxel (n=397)	% without progressive disease at 2 years non-inferiority	% without progressive disease at 2 years: 40% PFS: 19.1 mth	none					EORTC QLQ +13 end of treatment	Gr 3-4 infections 23 vs 36% Gr 3-4 neutropenia 22 vs 36% Gr 3-4 thrombocytopenia 1 vs 13% Gr 3-4 nausea 14 vs 6% Gr 3-4 neuropathy 14 vs 7%	4
GOG 158 / Ozols [33]	2003	Stage III after debulking (RM < 1 cm)	Cisplatin / paclitaxel (n=400) vs carboplatin / paclitaxel (n=392)	PFS non-inferiority	19.4 mth	none						Gr 3-4 gastrointestinal 23 vs 10% Gr 3-4 renal 3 vs 1% Gr 3-4 metabolic 8 vs 3% Gr 3-4 trombocytopenia 5 vs 39%	3
OV-10 / Piccart [34]	2003	Stage IIB-IV after debulking	Cisplatin / cyclophosphamide (n=338) vs cisplatin / paclitaxel (n=324)	OS / % alive at 6.5 years Crossover				Approx 36 mth	11% absolute OS gain at 6.5 years	0.75 (0.63-0.90)			4
DuBois [35]	2014	Maintenance stage III-IV EOC, PPC, FTC after debulking and 5 cycles carboplatin / paclitaxel (RM > 2 cm)	Placebo (n=468) vs pazopanib (n=472)	PFS	12.3 mth	5.6 mth	0.77 (0.64-0.91)					Treatment discontinuation 5.6 vs 33.3 %	2

Table 3
Trials showing no statistically significant benefit and therefore not scored on the ESMO-MCBS. * if no tumor type specified only EOC patients were included; # preliminary score of '1' but downgrade for worse QoL; cm = centimeters; EOC = epithelial ovarian cancer; FTC = fallopian tube cancer; ip = intraperitoneal; iv = intravenous; PFS = progression free survival; PPC = primary peritoneal cancer; (p)(c)CR = (pathologic)(clinical)complete response; OS = overall survival; QoL = quality of life; RM = residual mass; vs = versus.

Trial name/first author	Year	Setting*	Drug control vs intervention (n)	Primary outcome
Cisplatin vs carboplatin				
Swenerton [36]	1992	Any stage with macroscopic residual disease after debulking	Cisplatin/cyclophosphamide (n = 210) vs carboplatin/cyclophosphamide (n = 207)	PFS
Meerpohl [37]	1997	Stage III-IV after debulking (RM < 2 cm)	Cisplatin/cyclophosphamide (n = 77) vs carboplatin/cyclophosphamide (n = 81)	PFS
Neijt [38]	2000	Stage IIB-IV after debulking	Cisplatin/paclitaxel (n = 108) vs carboplatin/paclitaxel (n = 100)	PFS
Aravantinos [39]	2005	Stage IIC-IV after debulking	Paclitaxel/carboplatin (n = 121) vs paclitaxel/alternating carboplatin/cisplatin (n = 126)	OS
SCOTROC 4/Banerjee [40]	2013	Stage IC-IV EOC, FTC or PPC after debulking	Carboplatin flat dose (EOC n = 407) vs carboplatin dose escalation (EOC n = 407)	PFS
Paclitaxel				
GOG 132/Muggia [41]	2000	Stage III-IV after debulking (RM > 1 cm)	Cisplatin (n = 200) vs paclitaxel (n = 213) vs cisplatin/paclitaxel (n = 201)	PFS
ICON3 [42]	2002	Any stage after debulking, requiring chemotherapy according to physician	Paclitaxel/carboplatin (n = 478) vs carboplatin (n = 943) and paclitaxel/carboplatin (n = 232) vs cyclophosphamide/doxorubicin/cisplatin (n = 539)	OS
Spriggs [43]	2007	Stage III-IV EOC, FTC, PPC after debulking	Cisplatin/paclitaxel 24 h (n = 140) vs cisplatin/paclitaxel 96 h infusion (n = 140)	PFS
Other cytostatics				
Skarlos [44]	1996	Stage IIC-IV	Carboplatin (n = 73) vs carboplatin/epirubicin/cyclophosphamide (n = 57)	cCR
Wadler [45]	1996	Stage III-IV after debulking or stage I-II with progressive disease or residual disease after irradiation	Melphalan (n = 118) vs cyclophosphamide/hexamethylmelamine/doxorubicin/cisplatin (n = 126)	Clinical response rate
Wils [46]	1999	Stage IC-IV after debulking	Cyclophosphamide/epirubicin/cisplatin (n = 94) vs epirubicin/cisplatin (n = 97)	pCR
SCOTROC 1/Vasey [47]	2004	Stage IC-IV EOC and PPC after debulking	Carboplatin/paclitaxel (n = 538) vs carboplatin/docetaxel (n = 539)	PFS
Du Bois [48]	2006	Stage IIB-IV after debulking	Carboplatin/paclitaxel (n = 635) vs carboplatin/paclitaxel/epirubicin (n = 647)	OS
HIDOC-EIS/Möbus [49]	2007	Stage IIB-IV after debulking	Carboplatin/paclitaxel (n = 71) vs high-dose chemotherapy and peripheral blood stem cell support (n = 78)	PFS
GOG182-ICON 5/Bookman [50]	2009	Stage III-IV EOC and PPC after debulking	Carboplatin/paclitaxel (N = 864) + gemcitabine (n = 864) or liposomal doxorubicin (n = 862) or topotecan (n = 861)	OS
Bolis [51]	2010	Stage III-IV after debulking (RM > 1 cm)	Carboplatin/paclitaxel (n = 170) vs carboplatin/paclitaxel/topotecan (n = 156)	OS
Du Bois [52]	2010	Stage I-IV after debulking	Carboplatin/paclitaxel (n = 882) vs carboplatin/paclitaxel/gemcitabine (n = 862)	OS
Hoskins [53]	2010	Stage IIB-IV EOC, FTC or PPC after debulking	Carboplatin/paclitaxel 8 cycles (n = 410) vs cisplatin/topotecan 4 cycles and carboplatin/paclitaxel 4 cycles (n = 409)	PFS
MITO-2/Pignata [54]	2011	Stage IC-IV after debulking	Carboplatin/paclitaxel (n = 410) vs carboplatin/peg-liposomal doxorubicin (n = 410)	PFS
Fruscio [55]	2011	Stage III-IV after debulking	Cisplatin 3 weekly 6 cycles (n = 139) vs cisplatin weekly 9 cycles (n = 146)	PFS
Lindemann [56]	2012	Stage IIB-IV EOC, PPC or FTC after debulking	Carboplatin/paclitaxel (n = 442) vs carboplatin/paclitaxel/epirubicin (n = 445)	PFS
Antihormonal therapy				
Emons [57]	1996	Stage III-IV	Placebo (n = 66) vs triptorelin (n = 69)	OS
Immunomodulators				
Windbichler [58]	2000	Stage IC-IVa after debulking	Cyclophosphamide/cisplatin (n = 68) vs cyclophosphamide/cisplatin/gamma-interferon (subcutaneous) (n = 65)	PFS
Alberts [59]	2008	Stage III-IV EOC or PPC after debulking	Carboplatin/paclitaxel (n = 421) vs carboplatin/paclitaxel/interferon-gamma (n = 426)	OS
Lhommé [60]	2008	Stage III-IV EOC or PPC after debulking (RM > 1 cm)	Carboplatin/paclitaxel (n = 381) vs carboplatin/paclitaxel/valspodar (n = 381)	PFS
Angiogenesis inhibitors				
AGO-OVAR12/Du Bois [61]#	2016	Stage IIB-IV after debulking	Carboplatin/paclitaxel/placebo (n = 455) vs carboplatin/paclitaxel/nintedanib (n = 911)	PFS
Maintenance therapy				
EORTC 55875/Piccart [62]	2003	Maintenance after debulking and platinum-based chemotherapy (pCR)	Cisplatin ip (n = 76) vs no further treatment (n = 76)	OS
Markman [63]	2003	Maintenance EOC, PPC, FTC after debulking and platinum-based therapy (cCR)	Paclitaxel 3 (n = 128) vs 12 months (n = 134) after complete remission	PFS
MITO-1/De Placido [64]	2004	Maintenance after debulking and 6 cycles carboplatin/paclitaxel	Observation (n = 136) vs topotecan (n = 137)	PFS
Nicoletto [65]	2004	Maintenance after debulking and 5 cycles first line chemotherapy (pCR)	Observation (n = 61) vs 3 courses cisplatin/5-FU (n = 61)	PFS
Hall [66]	2004	Maintenance after debulking and first line chemotherapy	Observation (n = 149) vs interferon-alpha (n = 149)	OS
Alberts [67]	2006	Maintenance stage III after debulking and first line chemotherapy (pCR)	Observation (n = 35) vs interferon-alpha (n = 35)	PFS

(*continued on next page*)

Table 3 (*continued*)

Trial name/first author	Year	Setting*	Drug control vs intervention (n)	Primary outcome
Hirte [68]	2006	Maintenance stage III-IV after debulking and 6–9 cycles carboplatin/paclitaxel (cCR or RM < 2 cm)	Placebo (n = 121) vs tanomastat (n = 122)	PFS
Pecorelli [69]	2009	Maintenance stage IIB-IV after debulking and 6 cycles paclitaxel/platinum (c/pCR)	Observation (n = 99) vs 6 courses paclitaxel (n = 101)	PFS
Berek [70]	2009	Maintenance stage III-IV after debulking and firstline chemotherapy (cCR)	Placebo (n = 120) vs oregovomab (n = 251)	PFS
MIMOSA/Sabbatini [71]	2013	Maintenance stage III-IV EOC, FTC or PPC after debulking and firstline chemotherapy (cCR)	Placebo (n = 295) vs abagovomab (n = 593)	PFS

Table 4a
Cochrane Institute checklist for validity scores of trials on ip chemotherapy, dose-dense paclitaxel and bevacizumab. Corresponding question Cochrane validity checklist answered with: √ = yes, – = no, ? = unknown (question not answered in referred publication).

Study	Power analysis	Validity items										
		1	2	3	4	5	6	7	8	9	10	Total
Intraperitoneal chemotherapy												
Alberts [20]	√	√	?	–	–	√	√	√	√	√	–	6
van Driel [21]	√	√	?	–	–	√	√	√	–	√	√	6
Kirmani [22]	–	√	√	–	–	√	–	–	–	√	–	4
Gadducci [23]	√	√	√	–	–	–	–	√	√	√	–	5
Dose-dense paclitaxel												
JGOG 3016 [24]	√	√	√	–	–	√	√	√	√	√	√	8
Pignata [25]	√	√	√	–	?	√	√	√	√	√	√	8
Chan [26]	√	√	?	–	?	√	√	√	√	–	–	5
ICON8 [27]	Trial results not published											
Bevacizumab												
GOG 218 [28]	√	√	√	√	√	√	√	√	√	√	–	9
ICON7 2015 [29]	√	√	√	–	–	√	√	√	√	√	–	7

Table 4b
Cochrane Institute checklist for validity scores of trials on other treatments. Corresponding question Cochrane validity checklist answered with: √ = yes, – = no, ? = unknown (question not answered in referred publication).

Study	Power analysis	Validity items										
		1	2	3	4	5	6	7	8	9	10	Total
Hannigan [30]	√	√	√	–	–	√	√	√	√	√	?	7
Taylor [31]	√	√	?	–	–	√	√	?	√	√	?	5
Du Bois [32]	√	√	√	–	–	√	√	√	√	√	–	7
Ozols [33]	√	√	√	–	–	√	√	√	–	√	?	6
Piccart [34]	√	√	√	–	–	√	√	√	√	√	–	7
Du Bois [35]	√	√	√	√	√	√	√	√	√	√	–	9
Swenerton [36]	√	√	√	–	–	√	√	√	√	√	–	7
Meerpohl [37]	√	√	?	–	–	–	√	–	–	√	–	3
Neijt [38]	√	√	?	–	–	√	√	√	√	√	–	6
Aravantinos [39]	√	√	?	–	–	√	–	√	√	√	–	5
SCOTROC4 [40]	√	√	√	–	–	√	√	√	√	√	√	8
GOG 132 [41]	√	√	√	–	–	–	√	√	–	√	√	6
ICON3 [42]	√	√	√	–	–	√	√	√	√	√	√	8
Spriggs [43]	√	√	√	–	–	√	√	√	√	√	–	7
Skarlos [44]	√	√	√	–	–	√	√	√	√	√	–	7
Wadler [45]	–	√	?	–	–	√	√	√	–	√	?	5
Wils [46]	√	√	?	?	?	–	√	√	–	√	–	4
SCOTROC1 [47]	√	√	√	–	–	√	√	√	√	–	–	6
Du Bois 2006 [48]	√	√	√	–	–	√	√	√	√	√	–	7
HIDOC-EIS [49]	√	√	?	–	–	√	√	√	√	√	–	6
ICON5 [50]	√	√	√	–	–	√	√	√	–	√	–	6
Bolis [51]	√	√	√	–	–	√	√	–	√	√	–	6
Du Bois 2010 [52]	√	√	√	–	–	√	√	√	√	√	–	7
Hoskins [53]	√	√	√	–	–	√	√	√	√	√	√	8
MITO-2 [54]	√	√	√	–	–	√	√	√	√	√	–	7
Fruscio [55]	√	√	?	–	–	√	√	√	√	√	?	6
Lindemann [56]	√	√	√	–	–	√	√	√	√	√	–	7
Emons [57]	√	√	√	√	√	√	√	–	√	√	–	8
Windbichler [58]	–	√	√	–	–	√	√	√	√	√	–	7
Alberts 2008 [59]	√	√	√	–	–	√	√	√	√	√	–	7
Lhommé [60]	√	√	√	–	–	√	√	√	–	√	–	6
AGO-OVAR12 [61]	√	√	√	√	√	√	√	√	–	–	–	8
EORTC 55875 [62]	√	√	?	–	–	√	√	√	√	√	–	6
Markman [63]	√	√	?	–	–	√	√	√	√	√	–	6
MITO-1 [64]	√	√	√	–	–	√	√	√	√	√	–	7
Nicoletto [65]	–	√	?	–	–	–	√	√	√	√	–	5
Hall [66]	√	√	√	–	–	√	√	√	√	√	–	7
Alberts 2006 [67]	√	√	√	–	–	√	√	√	√	√	–	7
Hirte [68]	√	√	√	√	?	√	√	√	√	√	–	8
Pecorelli [69]	√	√	√	–	–	√	√	√	√	√	–	7
Berek [70]	√	√	√	√	√	√	√	–	√	√	–	8
MIMOSA [71]	√	√	√	√	√	√	√	√	√	√	–	9

example are the NCCN Evidence Blocks developed to visualise the key measures that form the basis of the recommendations in the NCCN clinical practice guidelines [86].

A major caveat is that ESMO-MCBSv1.1 scores are only calculated for studies showing either a statistically significant survival benefit of the studied treatment, or non-inferior survival but better QoL or less clinically significant grade 3–4 toxicities. Negative studies could be overlooked in treatment advices and guidelines, because of this selection bias. However, keeping this in mind, summarising the clinical benefit of different treatment strategies using the ESMO-MCBS does provide a quick overview of the available body of evidence. A comparable analysis of second and third line treatments could therefore be considered.

Conclusion and future perspectives

Based on ESMO-MCBS scores, dose-dense paclitaxel and intraperitoneal chemotherapy cannot be recommended as standard first line treatment in advanced ovarian cancer. Bevacizumab can be considered in the high-risk population, but is debated because an OS benefit was only shown in this subgroup of patients. The current standard first line treatment in advanced ovarian cancer, combination chemotherapy with carboplatin and paclitaxel, is strongly supported by ranking of the available evidence on the ESMO-MCBSv1.1. ESMO-MCBSv1.1 thresholds for clinical benefit, including QoL analyses and reporting of hazard ratios, should be taken into account in designing future clinical trials.

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Conflicts of interest

The authors KE Broekman, M Jalving, H van Tinteren, C Sessa and AKL Reyners declare that they have no competing interests.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at https://doi.org/10.1016/j.ctrv.2018.06.008.

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